ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

TOPAMAX®

(topiramate)

Tablets

(100, 200,

NDA 20-505

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF NEUROPHARMACOLOGICAL
DRUG PRODUCTS (HFD-120)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-505

TOPAMAX®

(topiramate)

Tablets

The Food and Drug Administration (FDA) recognizes the National Environmental Policy Act of 1969 (NEPA) as the national charter for protection, restoration, and enhancement of the environment. NEPA establishes policy, sets goals (section 101), and provides procedures (section 102) for carrying out the policy.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for **TOPAMAX®**, **The R.W. Johnson Pharmaceutical Research Institute** has conducted a number of environmental studies and prepared an environmental assessment in accordance with 21 CFR 25.31a(a) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Topiramate is a synthetic drug which is administered as an oral tablet in adjunctive therapy for partial onset seizures with or

The drug substance will be manufactured at

The drug product will be manufactured at McNeil Pharmaceutical, Dorado, PR. The finished drug product will be used in hospitals, clinics and homes.

Topiramate may enter the environment from patient use, disposal or from manufacturing operations. Chemical and physical test results indicate that the compound will most likely be restricted to the aquatic environment.

As topiramate is expected to persist in the aquatic environment for some time, the toxicity to organisms was characterized. Acute toxicity studies in water fleas (*Daphnia magna*) and blue gill fish (*Lepomis macrochirus*) and microbial toxicity testing indicate that the drug substance is not expected to be toxic at the expected environmental concentration.

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Returned and expired drug product is disposed of by incineration. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic procedures. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

11/19/95 Nancy B Sager
DATE

Prepared By
Nancy B. Sager
Acting Supervisor, Environmental Assessments
Center for Drug Evaluation and Research

11/20/95
DATE

Concurred
Roger L. Williams, M.D.
Deputy Center Director for Pharmaceutical Science
Center for Drug Evaluation and Research

Attachments: Environmental Assessment
(Note: Non-contiguous page numbering of EA document is the result of intermingled appendices being removed from the document, which do not need to be released (e.g., air permits).

V. ENVIRONMENTAL ASSESSMENT

1.0 DATE

February 1994 (Original)
December 1994 (1st Revision)

2.0 NAME OF APPLICANT/ PETITIONER

The R. W. Johnson Pharmaceutical Research Institute

3.0 ADDRESS

Welsh and McKean Roads
Spring House, PA 19477-0776
U.S.A.

4.0 DESCRIPTION OF THE PROPOSED ACTION

4.1 Need for Action

We are requesting approval of a New Drug Application (NDA) for TOPAMAX® (topiramate) 100 mg, 200 mg,
tablets for oral administration. Topiramate is an anticonvulsant compound classified as a sulfamate-substituted monosaccharide. TOPAMAX will be marketed as adjunctive therapy in patients with partial onset seizures

The usual total daily dose as adjunctive therapy is 200 mg/day to 600 mg/day in two divided doses. Some patients may require doses up to 1,600 mg/day.

4.2 Manufacturers of Drug Substance

U.S.A.

4.2.1.2 Administrative address

1

4.2.1.3

4.2.2

4.2.2.2

4.3 Name and Address of Manufacturer of Drug Product

McNeil Pharmaceutical
A Division of OMJ Pharmaceuticals, Inc.
KM 0.8, Route 698
P.O. Box 710
Dorado, PR 00646-0710

4.4 Usage and Disposal

Topiramate tablets will be dispensed from pharmacies as a prescription drug product to individuals throughout the United States. Disposal of prescribed product will be through use. Returned and rejected topiramate tablets will be sent to incinerators that are designed to treat waste pharmaceuticals. The incinerators used are generally operated at temperatures in excess of 1500 degrees F and have gas residence times greater than one second. In addition, the incinerators are equipped with air pollution control scrubbers and/or bag filters. This control equipment controls the emissions of acid gases and particulates that may be generated as by-products of incineration. All are permitted by their respective environmental regulatory agencies to treat pharmaceutical wastes, such as topiramate and packaging.

Incinerators used by McNeil Pharmaceutical in the past include ones

4.5 Type of Environment Present and Adjacent to Manufacturing and Disposal Locations

The McNeil Pharmaceutical facility in Puerto Rico is located in a commercial and residential area, in a flat to hilly region, on the Northern coast of the island. The climate is tropical.

The incineration facilities that have been used for the disposal of returned goods, rejected goods, and residual manufacturing wastes are located in Louisiana, Alabama, South Carolina, and New York. These incinerator facilities are usually located in rural or commercial areas. The terrain surrounding these facilities varies from flat to hilly.

5.0 IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE THE SUBJECT TO THIS PROPOSED ACTION

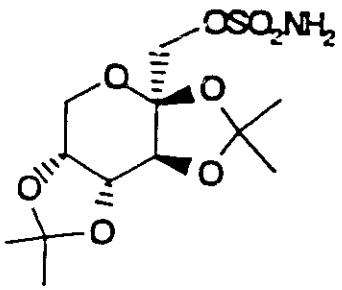
5.1 Active Ingredient

The active ingredient is topiramate.
CAS Registry Number: 97240-79-4

5.1.1 Chemical name

2,3:4,5-Bis-O-(1-methylethylidene)-β-D-fructopyranose sulfamate

5.1.2 Structural formula



5.1.3 Molecular formula

$C_{12}H_{21}NO_8S$

5.1.4 Molecular weight

339.36

5.1.5 General properties

Topiramate drug substance was evaluated for the following physical and chemical properties: organoleptics, crystallinity, thermal properties, hygrodynamics, dissociation (pKa) and partitioning, solubility, and solid state and solution stability. The results of these evaluations are summarized below and in the Data Summary Chart appended at the end of this section on page 03-02930. Please refer to Appendix A located on pages 03-03064 to 03-03103 for a detailed report of the physical and chemical properties of topiramate.

5.1.5.1 Organoleptics

Topiramate is a white granular powder. It has a slight odor and is bitter tasting.

5.1.5.2 Crystallinity

Topiramate has an X-ray powder diffraction (XRD) pattern that is typical of a crystalline organic compound

5.1.5.3 Thermal properties

The mean capillary melting range of 12 lots of topiramate drug substance is between 124.5 and 125.5 degrees C.

5.1.5.4 Hygrodynamics

Topiramate is neither hygroscopic or deliquescent.

5.1.5.5 Dissociation and partitioning

Topiramate is a weak acid. The pKa is 8.61 at 25 degrees C and 8.53 at 37 degrees C. The n-octanol/water partition coefficient is 3.74 at 25 degrees C. The log of the n-octanol/water partition coefficient is 0.57.

5.1.5.6 Solubility

The solubility of topiramate in water is 9.8 mg/mL at approximately 25 degrees C.

5.1.5.7 Solid-state and solution stability

Accelerated degradation studies were conducted with topiramate to determine the solid-state and solution stability of the drug substance and its route of degradation. A detailed report of these studies is provided in Appendix B on pages 03-03104 to 03-03231.

The results from these studies indicate that topiramate degrades in aqueous solution by hydrolysis. The degradation proceeds first by hydrolysis of the sulfamate to give diacetone fructose along with sulfamic and sulfuric acids. Hydrolysis of the acetonides of diacetone fructose gives rise to two possible mono-acetonides and to fructose. The hydrolysis half-life of topiramate is calculated to be approximately 80 days at pH 8 and 35 degrees C. The fructose can then undergo acid catalyzed degradation.

Degradation of topiramate in the solid state appears to follow the same mechanism as that observed in solution. The solid state degradation has been shown to be accelerated by heat and by humidity. The degradation of topiramate in solid state is extremely temperature dependent with degradation seen only at high temperatures (50 degrees C and above). Drug substance stored at room temperature has not been observed to degrade over a two year period.

5.2 Inactive Ingredients

Lactose Hydrous, NF
Pregelatinized Starch, NF
Microcrystalline Cellulose, NF
Sodium Starch Glycolate, NF
Magnesium Stearate, NF

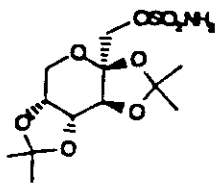
Carnauba Wax, NF
Purified Water, USP

Material Safety Data Sheets for all ingredients except Purified Water, USP are included at the end of this section on pages 03-02931 to 03-02976.

5.3 Packaging Materials

Topiramate tablets will be packaged in opaque high-density polyethylene (HDPE) bottles with child-resistant polypropylene closures with white pulpboard liners. Aluminum foil induction seal and an outer shrink seal will be used to make the product tamper-evident. Silica gel desiccant canisters are placed in the bottles and pharmaceutical grade cotton is added to cushion the tablets. Paperboard cartons and corrugated boxes are used for secondary packaging.

DATA SUMMARY CHART

COMPOUND	TOPIRAMATE	CAS Number: 97240-79-4
STRUCTURAL FORMULA		
MOLECULAR FORMULA	C12H21NO8S	
MOLECULAR WEIGHT	339.36	
ORGANOLEPTICS	white granular powder with a slight odor and slightly bitter taste	(APPENDIX A)
CRYSTALLINITY	has an X-ray powder diffraction (XRD) pattern that is typical of a crystalline organic compound.	(APPENDIX A)
THERMAL PROPERTIES	melting point between 124.5 and 125.5 degrees C.	(APPENDIX A)
HYGRODYNAMICS	neither hygroscopic nor deliquescent	(APPENDIX A)
DISSOCIATION	pKa = 8.61 at 25 degrees C	(APPENDIX A)
N-OCTANOL/WATER PARTITION COEFFICIENT	log (P) = 0.57 at 25 degrees C	(APPENDIX A)
SOLUBILITY	9.8 mg/mL in water	(APPENDIX A)
VAPOR PRESSURE	0.0000008 torr	(APPENDIX C)
HYDROLYSIS	-In water, hydrolyzes to fructose and sulfates -hydrolysis half-life is 80 days at pH 8 and and 35 degrees C	(APPENDIX B)
MICROBIAL TOXICITY	threshold inhibition concentration determined to be > 10 mg/L EC50> 100 mg/L	(APPENDIX D)
BIODEGRADATION	no biodegradation observed in 28 day screening studies	(APPENDIX D)
ACUTE TOXICITY TO DAPHNIDS (Daphnia magna)	48 hour EC50 > 1000 mg/L No Observed Effect Concentration (NOEC) = 1000 mg/L	(APPENDIX E)
ACUTE TOXICITY TO BLUEGILL SUNFISH (Lepomis macrochirus)	96 hour LC50 > 2400 mg/L No Observed Effect Concentration (NOEC) < 75 mg/L	(APPENDIX F)

MATERIAL SAFETY DATA SHEET

Chemical: TOPIRAMATE

CAS Number: 0097240794 Issue Date: 4/5/93

SECTION 1 - CHEMICAL IDENTIFICATION

COMPANY: R.W. JOHNSON P.R.I.
WELSH AND MCKEAN ROADS
SPRING HOUSE, PA 19477
Emergency Contact: DONNA S. HEIDEL, CIH Emergency Phone: 215-628-5000

Chemical Family: MONOSACCHARIDE DERIVATIVE
Chemical Formula: C12H21NO8S
Molecular Weight: 339.36

Synonyms: 2,3:4,5-BIS-O-(1-METHYLETHYLIDENE)-B-D-FRUCTOPYRANOSE SULFAMATE
MCN4853
RWJ-17021-000

J&J Hazard Rating - Health: (2) Moderate
- Fire: (2) Moderate
- Reactivity ( ) Not Est

Acute Toxicity - Oral: (2) Moderate
- Skin: (0) Negligible
- Eyes: (0) Negligible
- Inhalation: ( ) Not Est

Carcinogenicity: NTP: No IARC Monographs: No OSHA Regulated: No

Special Hazards: SUSPECT TERATOGEN

SECTION 2 - CHEMICAL COMPONENTS

Component: TOPIRAMATE
CAS Number: 0097240794 PERCENT OF MIXTURE: 100.0%

OSHA FINAL PEL-TWA:
NOT ESTABLISHED

OSHA FINAL PEL-STEL:
NOT ESTABLISHED

ACGIH TLV:
NOT ESTABLISHED

Chemical: TOPIRAMATE

CAS Number: 0097240794

Issue Date: 4/5/93

SECTION 2 - CHEMICAL COMPONENTS

Component: TOPIRAMATE
CAS Number: 0097240794 PERCENT OF MIXTURE: 100.0%

ACGIH STEL:
NOT ESTABLISHED

SECTION 3 - PHYSICAL DATA

Boiling Point (Deg.C): UNKNOWN
Melting Point (Deg.C): 125-126
Vapor Pressure (mm of Hg): NOT APPLICABLE
Vapor Density (Air=1): n/a
Specific Gravity: 0.00000
Packing Density: UNKNOWN
Solubility (H2O): 1%
Percent Volatiles: NONE
Evaporation Rate: NOT APPLICABLE

pH of 6.7 THRU 6.7 at a Concentration of 1%, ppm

Appearance: WHITE CRYSTALLINE SOLID WITH A BITTER TASTE.

Odor: NONE.

Odor Threshold: NOT APPLICABLE ppm

SARA Hazards: Acute: No Chronic: No Fire: No Pressure: No Reactive: No

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SECTION 4 - FIRE FIGHTING & EXPLOSION DATA

Flash Point (Deg.F): UNKNOWN

Autoignition (Deg.F): UNKNOWN

Lower Explosive Limit: UNKNOWN % in air

Upper Explosive Limit: UNKNOWN % in air

FIRE AND EXPLOSION HAZARDS: MODERATE FIRE OR EXPLOSION HAZARD. DUSTY CONDITIONS MAY CAUSE AN EXPLOSION WITH AN IGNITION SOURCE. TOPIRAMATE, WHEN SUSPENDED IN AIR, IS MODERATELY EXPLOSIVE, WITH A MAXIMUM EXPLOSION PRESSURE OF 9.3 BAR AND Kst VALUE OF 214 BAR M.S.-1.

EXTINGUISHING MEDIA: USE ANY MEDIA WHICH IS SUITABLE FOR THE SURROUNDING FIRE.

Chemical: TOPIRAMATE

CAS Number: 0097240794

Issue Date: 4/5/93

SECTION 4 - FIRE FIGHTING & EXPLOSION DATA

SPECIAL FIRE FIGHTING INSTRUCTIONS: SELF-CONTAINED BREATHING APPARATUS MAY BE NECESSARY. FIRE FIGHTING SHOULD BE DONE FROM A DISTANCE OR PROTECTED PLACE. USE WATER SPRAY TO COOL FIRE-EXPOSED CONTAINERS.

SECTION 5A - HEALTH HAZARDS & FIRST AID - INHALATION

ROUTES OF EXPOSURE & EFFECTS - INHALATION: NONE KNOWN.

FIRST AID - INHALATION: REMOVE TO FRESH AIR. ADMINISTER OXYGEN IF NECESSARY. GET IMMEDIATE MEDICAL ATTENTION.

SECTION 5B - HEALTH HAZARDS & FIRST AID - SKIN

ROUTES OF EXPOSURE & EFFECTS -SKIN: NONE KNOWN. NO DATA IS AVAILABLE TO INDICATE THAT TOPIRAMATE IS A SKIN IRRITANT IN HUMANS.

FIRST AID - SKIN: REMOVE CONTAMINATED CLOTHES IMMEDIATELY. WASH CONTAMINATED AREAS THOROUGHLY WITH SOAP AND WATER. USE EMERGENCY SHOWER TO REMOVE EXTENSIVE BODY CONTAMINATION. CONSULT A PHYSICIAN IF REDNESS OR IRRITATION PERSISTS.

SECTION 5C - HEALTH HAZARDS & FIRST AID - EYES

ROUTES OF EXPOSURE & EFFECTS - EYES: NONE KNOWN.

FIRST AID - EYES: FLUSH EYES IMMEDIATELY WITH WATER FOR AT LEAST 15 MINUTES. CONTACT A PHYSICIAN.

SECTION 5D - HEALTH HAZARDS & FIRST AID - INGESTION

ROUTES OF EXPOSURE & EFFECTS - INGESTION: INGESTION OF THIS MATERIAL MAY CAUSE HEADACHE; DIZZINESS; NAUSEA; VOMITING; NERVOUSNESS; TREMOR; DIFFICULTY WITH MEMORY; MOOD CHANGES; BEHAVIORAL CHANGES; AND REPRODUCTIVE SYSTEM EFFECTS. SUSPECT HUMAN TERATOGEN.

LD50 (female rats) : 2436mg/kg oral

FIRST AID - INGESTION: IF SWALLOWED CONTACT A PHYSICIAN.

Chemical: TOPIRAMATE

CAS Number: 0097240794 Issue Date: 4/5/93

SECTION 5E - GENERAL HEALTH EFFECTS - COMMENTS

TOPIRAMATE IS AN INVESTIGATIONAL DRUG; THEREFORE EFFECTS IN HUMANS MAY NOT BE FULLY CHARACTERIZED. SINCE TOPIRAMATE IS A CNS COMPOUND AND CAN CAUSE FATIGUE, MEMORY LOSS, CONFUSION, DIZZINESS, TREMOR, MOOD CHANGES AND BEHAVIORAL CHANGES, THERE IS A POTENTIAL DANGER FROM OPERATING MACHINERY, AUTOMOBILES, OR ENGAGING IN OTHER POTENTIALLY DANGEROUS ACTIVITIES IF EXPOSED TO THIS COMPOUND.
TOPIRAMATE HAS BEEN SHOWN TO CAUSE TERATOGENIC EFFECTS AND EMBRYO/FETAL TOXICITY IN RATS AND MICE. PREGNANT WOMEN, OR THOSE WHO MAY BE PREGNANT, SHOULD NOT HANDLE THIS MATERIAL. TOPIRAMATE IS NOT CONSIDERED TO BE MUTAGENIC IN THE AMES SALMONELLA/MICROSOMAL ACTIVATION ASSAY, THE PRIMARY RAT HEPATOCYTE/DNA REPAIR ASSAY, THE MOUSE LYMPHOMA MUTATION ASSAY, THE E. COLI BACTERIAL/MICROSOMAL ACTIVATION ASSAY, IN VITRO CYTOGENETICS ASSAY, AND IN AN IN VIVO RAT BONE MARROW CYTOGENETICS ASSAY.
TOPIRAMATE IS NOT CARCINOGENIC IN LABORATORY ANIMALS.

SECTION 5F - HEALTH CONDITIONS AGGRAVATED BY EXPOSURE

HEALTH CONDITIONS AGGRAVATED BY EXPOSURE: FEMALES WHO ARE OR MAY BE PREGNANT SHOULD NOT HANDLE OR BE EXPOSED TO THIS MATERIAL. CONTACT YOUR HEALTH OFFICE FOR ADDITIONAL COUNSELING.

SECTION 6 - REACTIVITY & POLYMERIZATION

Stability: STABLE
Conditions to Avoid: ACID SOLUTIONS.

Incompatible Materials: ACIDS.
Hazardous Decomposition Products:
SULFUR, NITROGEN, AND CARBON OXIDES MAY BE LIBERATED WHEN TOPIRAMATE BURNS.
Hazardous Polymerization: WILL NOT OCCUR
Conditions to Avoid: STORAGE IN ACID SOLUTIONS.

SECTION 7 - SPILL, LEAK, & DISPOSAL PROCEDURES

STEPS TO BE TAKEN - SPILLS, LEAKS, OR RELEASE: EVACUATE AREA UNTIL DUST SETTLES. WEAR SKIN, EYE AND RESPIRATORY PROTECTION - SEE SECTION 8. CAREFULLY, SWEEP OR VACUUM UP INTO A SEALED WASTE CONTAINER. AVOID CREATING DUSTY CONDITIONS.

Chemical: TOPIRAMATE

CAS Number: 0097240794

Issue Date: 4/5/93

SECTION 7 - SPILL, LEAK, & DISPOSAL PROCEDURES

WASTE DISPOSAL METHODS: INCINERATE, ACCORDING TO FEDERAL, STATE AND LOCAL REGULATIONS.

SECTION 8 - SPECIAL PROTECTIVE EQUIPMENT

VENTILATION: LOCAL EXHAUST AT CONTAMINANT GENERATION POINTS. WHEN HANDLING SMALL AMOUNTS USE: LABORATORY HOOD. DO NOT RECIRCULATE EXHAUST AIR. AGGRESSIVE LOCAL EXHAUST VENTILATION REQUIRED TO REDUCE EXPOSURES TO AIRBORNE DUSTS BELOW THE J&J OCCUPATIONAL EXPOSURE LIMIT OF 0.01 mg/m3

PROTECTIVE EQUIPMENT - EYES: SAFETY GLASSES OR GOGGLES RECOMMENDED. DO NOT WEAR CONTACT LENSES IF RESPIRATORY PROTECTION IS REQUIRED.

PROTECTIVE EQUIPMENT - GLOVES: WHEN HANDLING THE SOLID OR POWDERED MATERIAL WEAR LATEX GLOVES. WHEN HANDLING ORGANIC SOLUTIONS WEAR SOLVENT IMPERVIOUS GLOVES.

PROTECTIVE EQUIPMENT - RESPIRATORS: WHEN HANDLING SMALL AMOUNTS A HIGH EFFICIENCY RESPIRATOR APPROVED FOR DUSTS, MISTS, FUMES, AND RADIONUCLIDES IS REQUIRED. WHEN HANDLING LARGE AMOUNTS POWERED AIR-PURIFYING RESPIRATOR APPROVED FOR DUSTS, MISTS, FUMES, AND RADIONUCLIDES IS REQUIRED. SUPPLIED AIR RESPIRTOR REQUIRED IN THE ABSENCE OF EFFECTIVE LOCAL EXHAUST VENTILATION FOR CONTROL OF AIRBORNE DUSTS. SELF-CONTAINED BREATHING APPARATUS REQUIRED FOR FIRES AND SPILLS.

PROTECTIVE EQUIPMENT - OTHER: DISPOSABLE COVERALLS (EG., TYVEK) FOR ROUTINE WORK.

SECTION 9 - SPECIAL PRECAUTIONS - STORAGE & HANDLING

STORAGE & HANDLING CONDITIONS: STORE AWAY FROM INCOMPATIBLE MATERIALS - SEE SECTION 6 ABOVE.

Do Not Store with: ACIDS

SECTION 10A - SHIPPING INFORMATION (49CFR/DOT)

Proper Shipping Name: N/A

Hazard Class: NONE LISTED

UN/NA Number: N/A

Labels (DOT): NONE REQUIRED

Packaging Exceptions: NONE KNOWN Packaging Requirements: NONE KNOWN

SECTION 11 - REFERENCE INFORMATION

NO INFORMATION ON FILE

Chemical: TOPIRAMATE

CAS Number: 0097240794

Issue Date: 4/5/93

SECTION 12 - MISCELLANEOUS COMMENTS

J&J OCCUPATIONAL EXPOSURE LIMIT: 0.01 MG/M3 AS AN EIGHT-HOUR TIME WEIGHTED AVERAGE

DISCLAIMER OF EXPRESSED AND IMPLIED WARRANTIES

Although reasonable care has been taken in the preparation of this document, R.W. JOHNSON P.R.I. extends no warranties and makes no representations as to the accuracy or completeness of the information contained therein, and assumes no responsibility regarding the suitability of this information for the user's intended purposes or for the consequences of its use. Each individual should make a determination as to the suitability of the information for their particular purpose(s).

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6.1.1.2 Wastewater

Wastewater is treated in a municipal wastewater treatment plant after neutralization. The plant routinely monitors and analyses the wastewater.

Substance in wastewater	kg/kg topiramate
TOTAL	

6.1.1.3 Air emissions

Air emission is controlled by a Central Scrubber System. No contaminant (< 0.05 kg/kg) is expected to be exhausted as a result of the manufacturing of topiramate drug substance. The drainage from the Central Scrubbing System goes to a municipal sewage purification plant.

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6.2 Manufacturing of Drug Product

Topiramate is not listed as a hazardous waste under the EPA Resource Conservation and Recovery Act (RCRA) of May 19, 1980, as amended.

6.2.1 Overview

A flow diagram showing the sequence of operations for the manufacturing of topiramate tablets is shown in Figure 1 on the following page

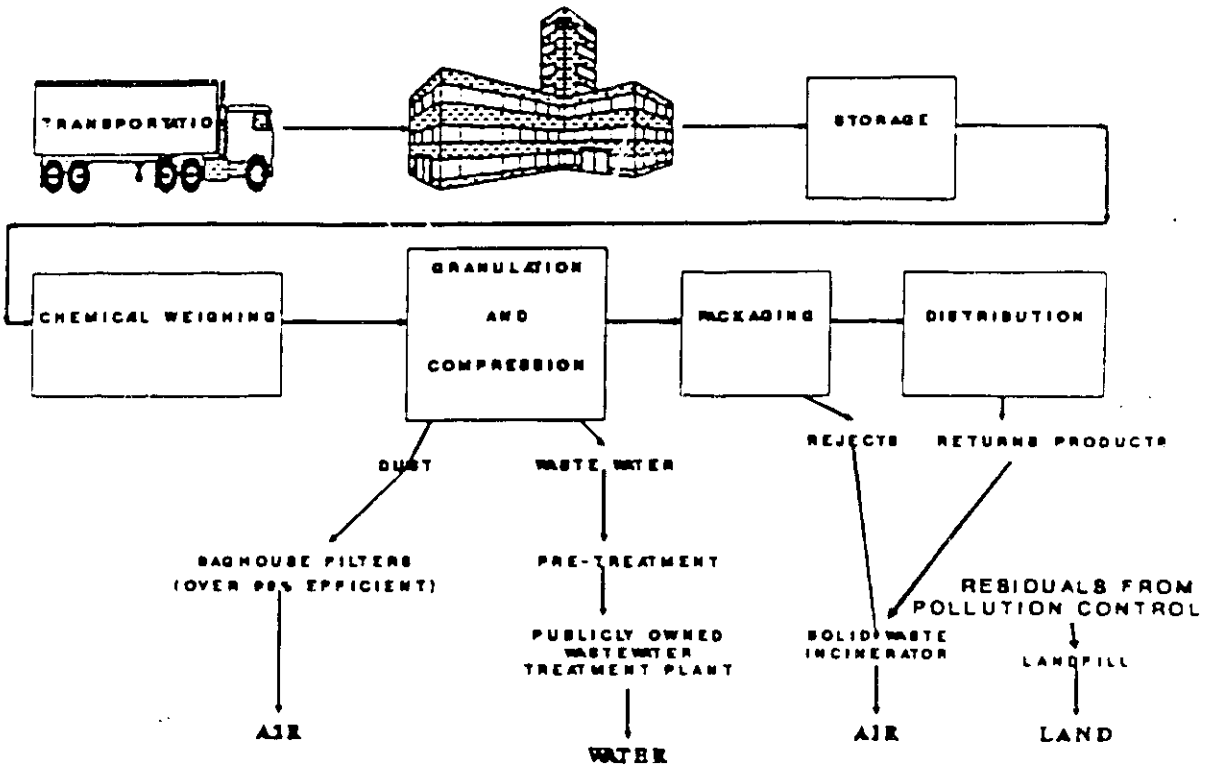
6.2.2 Transportation and storage

The raw materials for manufacturing the tablets are transported to the site from various suppliers. Materials are transported and stored in polyethylene bags. The polyethylene bags are protected against damage during handling by enclosure in a rigid outer protective container. Storage is in a dry area. No raw material is introduced into the environment during transportation and storage.

6.2.3 Chemical weighing

All solid materials in the process are weighed in an enclosed room. Dust generated in the operation is controlled at the point of generation and collected in fabric bag dust collectors. Such filters have efficiencies of greater than 99% in removing the entrained dust from the inlet air. The clean air is exhausted into the environment. Fabric filter systems at the McNeil Pharmaceutical facility at Dorado, PR, are covered under the air discharge permit issued by the Puerto Rico Environmental Quality Board (EQB). A copy of the air permit is included on pages 03-02992 to 03-03007. Manufacturing topiramate tablets is allowed under the existing air permit standards

Figure 1: Introduction of Substances into the Environment - Tablet Manufacturing



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6.2.5 Packaging

The drug product is packaged in opaque high-density polyethylene (HDPE) containers with child-resistant polypropylene closures with white pulpboard liner.

No drug product is expected to be discharged to air or water as a result of the packaging process. Rejected packaging materials are recycled or landfilled in permitted facilities. As recyclers of plastics and paper products become available, McNeil Pharmaceutical will seek ways to recycle more of the rejected packaging materials.

6.2.6 Warehouse and distribution

No drug product is expected to be discharged to air or water as a result of the warehouse and distribution process.

Any products returned to the distribution warehouse will be destroyed at permitted incineration facilities, such as those listed in Section 4.4.

6.3 Summary - Topiramate Introduced to the Environment as a Result of Tablet Manufacturing.

6.3.1 Production level basis

Based on projection kg/year is the maximum annual amount of the active drug to be produced during the first five years following product introduction.[1]

To assess the daily emissions, we can assume that each facility will process one batch per day. The largest batch contains kg of topiramate. Batch yields are typically greater than 97%. This results in less than of topiramate loss to the environment from all aspects of the production of each batch.[2]

6.3.2 Air emissions

Of the estimated maximum of of topiramate lost per batch, it is projected that is sent to fabric bag dust collectors. The dust collected is packaged for disposal as a non-hazardous waste. Such dust collectors have over 99% capture efficiencies, meaning that less than 0.05 kg of topiramate is discharged into the air environment per batch produced.

Topiramate is not volatile. The vapor pressure has been measured to be 3.84 X 10^{-6} torr. Please refer to Appendix C located on pages 03-03232 to 03-03252 for a detailed report of the vapor pressure of topiramate. Because of the water solubility of topiramate, the dust released into the air environment is expected to be washed into the water environment by rainfall.

6.3.3 Water discharges

It is expected that of topiramate per batch would be lost in equipment or lost during material transfer. Usually the material is vacuumed and packaged for disposal. However,

as a worst case scenario for wastewater discharge, we can assume that of topiramate is washed into the sewer during equipment cleaning. At the manufacturing location, the wastewaters flow to publicly owned wastewater treatment work (POTW). The POTW has secondary biological treatment to remove dissolved organics.

6.3.4 Discharge to land

It is expected that about of topiramate per batch would be rejects and would be disposed of as solid waste. Solid wastes from manufacturing, returned goods, and reject products are sent to incinerator sites such as those listed in Section The residues from the incinerators and any non-burnable materials are landfilled at government approved sites. Normally, no topiramate is released to the land as a result of tablet manufacturing.

6.4 Releases With Use

Topiramate is expected to enter the water environment as a result of use. The maximum expected emitted concentration (MEEC) is calculated below.[3]

Parts per million (ppm) in environment = A × B × C × D × E × F

where:

A = pounds/year product
B = year/365 days
C = day person/150 gallons
D = 1/(246 million persons-population of U.S.)
E = gallons/8.34 pounds
F = one million

Using) topiramate per year, the parts per million in the environment is calculated to be 0.00055 ppm. Based on the physical properties of topiramate, it will most likely be present in the water, rather than in the air or soil environment.

ORTHO-MCNEIL
PHARMACEUTICAL

Joseph T. Anstatt
Vice President, Operations

1000 Route 202, P.O. Box 300 Telephone 908-218-6000
Raritan, N.J. 08869-0602

December 2, 1994

To Whom It May Concern:

Ortho-McNeil states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production and packaging of Topiramate at its facility at Dorado, Puerto Rico. Ortho-McNeil also states that it is in compliance with emissions requirements set forth in federal, commonwealth and local statutes and regulations applicable to the production of Topiramate at its facility in Dorado Puerto Rico.

Sincerely,

C. T. Anstatt

Joseph T. Anstatt
Vice President, Operations

-03 03047

7.0 FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

The formulation is not volatile. Transfers from dust collectors are carried out in such a manner as to minimize dispersion. Typically, the dust is transferred to polyethylene lined fiber drums using collars or sleeves to prevent dispersion to the air. The preferred method of disposal is by incineration.

Material is not released directly to the soil, fresh water, estuarine or marine ecosystems as a result of the manufacturing operation.

Manufacturing operations are conducted according to all applicable Federal, State, and Local regulations, and current Good Manufacturing Practices (21 CFR 210-211), and are carefully monitored to minimize the potential for material loss during processing.

7.1 Fate of Topiramate

As shown in Sections 5.0 and 6.0 of this environmental assessment, topiramate is soluble in water (9.8 mg/mL or 0.0289 M). The log of the octanol/water partition coefficient is 0.57. It is not volatile. We expect that topiramate will be in the water ecosystem.

In the manufacturing process, a small amount (estimated to be less than 0.05 kg per batch) of topiramate dust is emitted from the air pollution control equipment. A copy of the air permit is located on pages 03-02992 to 03-03007. Normal housekeeping and maintenance procedures call for periodic inspections and cleaning around the air pollution control equipment. It is expected that topiramate dust would be vacuumed or swept up and disposed of as solid waste.

The topiramate generated from the clean out of air pollution control filters and any rejected materials are packaged and sent to permitted incinerator facilities for treatment. As indicated in Section 6.0 of this environmental assessment, a maximum o of topiramate per batch is expected to be disposed of as solid waste. In the incineration process, topiramate would be oxidized to carbon dioxide and water. The acid vapors produced in the incineration process would be scrubbed and neutralized.

Wastewater is generated from equipment cleaning. It is estimated that a maximum of 4.4 kg of topiramate per batch may be washed out from the clean-out.

7.1.1 Fate of Topiramate Manufactured at Dorado, Puerto Rico.

At the Dorado, PR facility, wastewater is pre-treated. Wastewater from the entire facility is pumped into an equalization tank to adjust pH, increase dissolved oxygen and add nutrients. The wastewater is then pumped into an aerobic sequential batch biological treatment system to reduce dissolved organic levels and to settle out solids. Wastewater from this pre-treatment process is discharged to the publicly owned treatment works operated by the Puerto Rico Aqueduct and Sewer Authority (PRASA). A copy of the most current PRASA permit is located on pages 03-03008 to 03-03046.

The PRASA treatment plant in the town of Dorado treats approximately 1.3 million gallons per day (mgd) of wastewater from industrial and residential sources.[4] Assuming a batch per day, the concentration of topiramate at the inlet of the PRASA wastewater treatment plant is calculated to be 0.89 mg/L. The plant has primary sedimentation and secondary trickling filters. The treated effluent is discharged into the LaPlata River. The river flows into the Atlantic Ocean about one mile downstream of the town of Dorado.

7.2 Results of Wastewater Treatability Testing

Topiramate was evaluated for its inhibitory effect on activated sludge. Following the inhibition test, a biodegradation screening study was conducted using microbial inocula from a variety of sources. The report of this testing conducted by is provided in Appendix D located on pages 03-03253 to 03-03299.

Topiramate did not inhibit microbial activity at a concentration of 10 mg/L or less. Approximately 18% microbial inhibition was observed at a concentration of 100 mg/L. The respiration rate of an activated sludge and synthetic sewage suspension, aerated for 3 hours in the presence of topiramate, was compared to the respiration rate of an activated sludge and synthetic feed suspension to which no test substance was added. A reference compound (3,5-dichlorophenol) was also tested as a positive control.

conducted a biodegradation screening study on topiramate. It was determined that topiramate is not biodegraded to carbon dioxide and water within the four week time limit of the screening tests. The screening tests used biological inocula from aerobic and anaerobic sources.

Drug degradation studies indicate that topiramate degrades in solution by hydrolysis. The degradation proceeds first by hydrolysis of the sulfamate group to give diacetone fructose and sulfamic/sulfuric acid. Hydrolysis of the acetonides of diacetone fructose gives rise to monoacetonides and to fructose. Although the stability testing was done at warm temperatures, the data indicate that hydrolysis still occurs at ambient temperatures but at a slower rate. The hydrolysis half-life of topiramate is calculated to be approximately 80 days at pH 8 and 35 degrees C. A detailed report of the degradation studies is provided in Appendix B located on pages 03-03104 to 03-03231.

There is sufficient information in the literature to establish that the hydrolysis product of topiramate, fructose, is biodegradable.

Based on the fate testing on topiramate, we expect that topiramate in the water environment will eventually hydrolyze to fructose and sulfur compounds. The fructose is readily biodegraded.

8.0 ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

8.1 Effect on Wastewater Treatment Plants

As provided in Section 7.2, the worst case maximum concentrations of topiramate at wastewater treatment plants serving the sites of manufacturing and at the plants serving the users of this product are not expected to have any toxic effect on the treatment plants' performance.

8.2 Acute Toxicity

performed a test to determine the acute toxicity of topiramate to Daphnia magna. The protocol from FDA Technical Assistance Document, Section 4.08, was followed. It is reported that the 48-hour EC_{50} or median effect concentration value is greater than 1,000 mg topiramate/L. The No Observed Effect Concentration (NOEC) was determined to be 1000 mg/L. The test report is provided in Appendix E on pages 03-03300 to 03-03357.

performed a test to determine the acute toxicity of topiramate to bluegill sunfish (Lepomis macrochirus). The protocol from the FDA Technical Assistance Document, Section 4.11 was followed. Two tests were conducted. During the first test, mortality was observed; however, the results were not sufficient to calculate an LC_{50}. During the second test, no mortality was observed. Effects were observed in the concentration range of 84 to 3,000 mg/L. These effects included darkened pigmentation and loss of equilibrium. The results of these two tests established that

topiramate is relatively non-toxic. Since no concentration produced ≥ 50% mortality, the 96-hour LC_{50} value was empirically estimated to be greater than 2400 mg/L, the highest mean measured concentration tested. The NOEC was determined to be less than 75 mg/L, the lowest mean measured concentration tested. The test report is provided in Appendix F on pages 03-03358 to 03-03424.

8.3 Effect at the Dorado, Puerto Rico, Site

In the worst case, if topiramate passes through the PRASA Dorado wastewater treatment plant without removal, the concentration at the treatment plant outfall is calculated to be 0.89 mg/L. (This is based on the plant's 1.3 million gallons/day of flow, and 4.4 kg/day of topiramate from the Dorado manufacturing.)

Effluent from the treatment plant would be further diluted in the receiving stream, the LaPlata River. The LaPlata River flows into the Atlantic Ocean about one mile downstream of the town of Dorado. Using the lowest seven day average flow in the last ten years (7Q10) for LaPlata River, the maximum concentration of topiramate in the stream is calculated to be 0.17 mg/L.[5]

The expected maximum concentrations are much less than the toxicity effect levels determined for Daphnia magna and for bluegill sunfish. We expect that topiramate in water would be degraded by hydrolysis into fructose and sulfur compounds (sulfates, sulfamates, etc.). The fructose would be further degraded in the environment by microbial activities. (See Section 7.2 for discussion on hydrolysis.)

8.4 Maximum Expected Emitted Concentration (MEEC)

The MEEC, calculated in Section 6 of this assessment, is determined to be 0.00055 mg/L. This is much less than the toxicity levels observed for Daphnia magna and for bluegill sunfish. We expect that topiramate in water would be degraded by hydrolysis into fructose and sulfur compounds (sulfates, sulfamates, etc.). The fructose would be further degraded in the environment by microbial activities.

9.0 USE OF RESOURCES AND ENERGY

Existing facilities are planned to be used for the production of this product. Based on producing batches per year, we estimate that the production of topiramate would require an additional 1340 kilowatt-hours per day of electricity and 2750 gallons of water per day. For comparison, this amount is less than 7 percent of the electricity and water used at the Dorado facility in 1991. These resource usages may even be lower since the facility is implementing conservation measures such as more efficient heating, air conditioning, and lighting.

It is expected that manufacturing topiramate will produce very little additional solid waste from the manufacturing site. No new facilities nor significant demand on natural resources would be needed for the disposal of additional solid wastes.

The production of topiramate is not expected to have any effects upon endangered or threatened species, or upon property listed in, or eligible for listing in the National Register of Historical Places. The land occupied by the McNeil Pharmaceutical facility in Dorado, Puerto Rico is located in an industrial area and the zoning map classification is I-1 (Light industry) and R-0 (Low population density residential). Therefore, we assume the land is not located where historical and archaeological properties, endangered or threatened species habitats are present.

10.0 MITIGATION MEASURES

Processing of this product will be in strict compliance with current Good Manufacturing Practices and Federal, State and Local requirements. The procedures outlined in Section 6 are sufficient to avoid any adverse environmental impact. Employees

McNeil Pharmaceutical in Dorado, Puerto Rico receive training on spill control, emergency response, and waste management. All three facilities have adequate spill control procedures and practices in place.

McNeil Pharmaceutical are pursuing opportunities to reduce solid waste generation, to recycle, and to conserve energy. Cardboard, office paper, aluminum cans, and clear glass bottles are currently being recycled. Efficient heating and air conditioning controls and upgrades have been installed at some of the facilities.

11.0 ALTERNATIVES TO THE PROPOSED ACTION

The primary alternative to the proposed action is that of no action, with the resulting deprivation to mankind of potentially beneficial therapy. We believe that alternatives to the proposed action are not needed, since no adverse environmental effect has been noted. Procedures are in place at the manufacturing sites to minimize the introduction of drug substance and other chemicals into the environment. The manufacturing, distribution, and usage of topiramate result in concentrations that are far below threshold effect levels for aquatic and terrestrial organisms tests. No impact is expected on endangered or threatened species, or upon properties listed in or eligible for listing in the National Register of Historical Places.

12.0 LIST OF PREPARERS

This document was prepared by N.S. Sandy Yee, Manager of Facility Services/Engineering, and Environmental Affairs at Ortho-McNeil Pharmaceutical, Spring House, PA 19477-0776. A current curriculum vitae (CV) is provided on the following pages.

13.0 CERTIFICATION

The undersigned official certifies that the information presented is true, accurate and complete to the best of the knowledge of Ortho-McNeil Pharmaceutical for the preparation of the environmental assessment.

ORTHO-MCNEIL PHARMACEUTICAL

BY:

N.S. Sandy Yee
Manager,
Facility Services/Engineering,
and Environmental Affairs

12/15/94
Date

COMPLETED

OCT 5 1995

OCT 0 5 1995

Topamax™ (topiramate)
100, 200, tablets
NDA 20-505
Reviewer: Iftekhar Mahmood, Ph. D.

R. W. Johnson Pharmaceutical Res Institute
Welsh & Mckean Road
Spring House, PA 19477-0776

Submission Dates: December 29, 1994, June 19, 1995, August 15, 1995, August 24, 1995, August 21, 1995.

Synopsis

Topamax™ (topiramate) is a chemical compound classified as a sulfamate-substituted monosaccharide, claimed by the Sponsor to be an antiepileptic. Chemically Topamax is designated as 2, 3:4,5-bis-O-(1-methylethylidene)-b-D-fructopyranose sulfamate. It will be available as 100 and 200 mg round tablets tablets for oral administration.

Topiramate is rapidly and well-absorbed after oral administration. Following 400 mg multiple oral dosing every 12 hours, peak plasma concentration of 27 µg/mL is reached in about two hours. There is no effect of food on the bioavailability of topiramate. The volume of distribution of topiramate following 100 to 1200 mg oral dose ranged from 0.55 l/kg to 0.8 l/kg. Plasma protein binding of topiramate is about 17 percent. Topiramate is not extensively metabolized and at least six minor inactive metabolites formed through hydroxylation, hydrolysis and glucuronidation have been identified from plasma and urine of humans. About 70% of the dose of topiramate is excreted unchanged in human urine. The mean elimination half-life of topiramate in humans is approximately 21 hrs. Oral clearance is approximately 29 ml/min in humans following oral administration. Clearance of topiramate was not affected by age, gender or race. The mean renal clearance of topiramate was 14 ml/min across 100-1200 mg single oral dose range and was 17 ml/min for 50 and 100 mg q12h dosing regimens.

Multiple q 12h dosing of 50 and 100 mg doses of topiramate for at least 14 days resulted in topiramate C_{max} and AUC values that increased in a linear and dose-proportional manner. Concomitant multiple-dose administration of topiramate 100-400 mg q12h (n =12) regimens with phenytoin and 100-600 mg q12h (n= 20) regimens with carbamazepine show dose proportional linear kinetics of topiramate. Likewise, topiramate showed dose proportionality between 100-600 mg q12h (n =3) regimens in the presence of primidone. Between 100 to 400 mg b.i.d.(n =12) dosing, both Cmax and AUC(0-12) of topiramate were 25% less than expected (slightly non-linear) at the 400 mg b.i.d. dose in the presence of valproic acid.